

TITLE OF THE INVENTION

ISOQUINOLINONE POTASSIUM CHANNEL INHIBITORS

BACKGROUND OF THE INVENTION

5 The present invention relates broadly to compounds that are useful as potassium channel inhibitors. Compounds in this class may be useful as Kv1.5 antagonists for treating and preventing cardiac arrhythmias, and the like, and as Kv1.3 inhibitors for treatment of immunosuppression, autoimmune diseases, and the like.

10 Voltage gated potassium channels (Kv) are multimeric membrane proteins composed of four α subunits and are often associated with accessory β subunits. Kv channels are typically closed at resting membrane potentials, but open upon membrane depolarization. They are involved in the repolarization of the action potential and thus in the electrical excitability of nerve and muscle fibers. The Kv1 class of potassium channels is comprised of at least seven family members, named Kv1.1, Kv1.3, Kv1.5, etc. Functional voltage-gated K^+
15 channels may exist either as homo-oligomers composed of identical subunits, or hetero-oligomers of different subunit composition. This phenomenon is thought to account for the wide diversity of K^+ channels. However, subunit compositions of native K^+ channels and the physiologic role that particular channels play are, in most cases, still unclear.

20 The Kv1.3 voltage-gated potassium channel is found in neurons, blood cells, osteoclasts and T-lymphocytes. Membrane depolarization by Kv1.3 inhibition has been shown to be an effective method to prevent T-cell proliferation and therefore has applications in many autoimmune conditions. Inhibition of K^+ channels in the plasma membrane of human T-lymphocytes has been postulated to play a role in eliciting immunosuppressive responses by regulating intracellular Ca^{++} homeostasis, which has been found to be important in T-cell
25 activation. Blockade of the Kv1.3 channel has been proposed as a novel mechanism for eliciting an immunosuppressant response (Chandy *et al.*, *J. Exp. Med.* 160: 369, 1984; Decoursey *et al.*, *Nature*, 307: 465, 1984). However, the K^+ channel blockers employed in these early studies were non-selective. In later studies, Margatoxin, which blocks only Kv1.3 in T-cells, was shown to exhibit immunosuppressant activity in both *in vitro* and *in vivo* models. (Lin *et al.*, *J. Exp.*
30 *Med.*; 177: 637, 1993). The therapeutic utility of this compound, however, is limited by its potent toxicity. Recently, a class of compounds has been reported that may be an attractive alternative to the above-mentioned drugs (U.S. Patent Nos. 5,670,504; 5,631,282; 5,696,156; 5,679,705; and 5,696,156). While addressing some of the activity/toxicity problems of previous drugs, these
35 compounds tend to be of large molecular weight and are generally produced by synthetic manipulation of a natural product, isolation of which is cumbersome and labor intensive.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is likely to increase in prevalence with the aging of the population. Conservative estimates indicate that AF affects >2 million Americans, represents over 5% of all admissions for cardiovascular diseases and leads to a 3- to 5-fold increase in the risk of stroke (Kannel et al, *Am. J. Cardiol.*, 82:2N-9 N, 1998). While AF is rarely fatal, it can impair cardiac function and lead to complications such as the development of congestive heart failure, thromboembolism, or ventricular fibrillation.

Reentrant excitation (reentry) has been shown to be a prominent mechanism underlying supraventricular arrhythmias in man (Nattel, S., *Nature*, 415:219-226, 2002).

Reentrant excitation requires a critical balance between slow conduction velocity and sufficiently brief refractory periods to allow for the initiation and maintenance of multiple reentry circuits to coexist simultaneously and sustain AF. Increasing myocardial refractoriness by prolonging action potential duration (APD) prevents and/or terminates reentrant arrhythmias. Action potential duration is determined by the contributions of the repolarizing potassium currents I_{Kr} , I_{Ks} , and I_{Kur} , and the transient outward current, I_{to} . Blockers of any one of these currents would therefore be expected to increase the APD and produce antiarrhythmic effects.

Currently available antiarrhythmic agents have been developed for the treatment of ventricular and atrial/supraventricular arrhythmias. Malignant ventricular arrhythmias are immediately life-threatening and require emergency care. Drug therapy for ventricular arrhythmia includes Class Ia (eg. procainamide, quinidine), Class Ic (eg. flecainide, propafenone), and Class III (amiodarone) agents, which pose significant risks of proarrhythmia. These Class I and III drugs have been shown to convert AF to sinus rhythm and to prevent recurrence of AF (Mounsey, JP, DiMarco, JP, *Circulation*, 102:2665-2670), but pose an unacceptable risk of potentially lethal ventricular proarrhythmia and thus may increase mortality (Pratt, CM, Moye, LA, *Am J. Cardiol.*, 65:20B-29B, 1990; Waldo et al, *Lancet*, 348:7-12, 1996; Torp-Pedersen et al, *Expert Opin. Invest. Drugs*, 9:2695-2704, 2000). These observations demonstrate a clear unmet medical need to develop safer and more efficacious drugs for the treatment of atrial arrhythmias.

Class III antiarrhythmic agents cause a selective prolongation of the APD without significant depression of cardiac conduction or contractile function. The only selective Class III drug approved for clinical use in atrial fibrillation is dofetilide, which mediates its anti-arrhythmic effects by blocking I_{Kr} , the rapidly activating component of I_K found in both atrium and ventricle in humans (Mounsey, JP, DiMarco, JP, *Circulation*, 102:2665-2670). Since I_{Kr} blockers increase APD and refractoriness both in atria and ventricle without affecting conduction per se, theoretically they represent potentially useful agents for the treatment of arrhythmias like

AF (Torp-Pedersen, et al, *Expert Opin. Invest. Drugs*, 9:2695-2704, 2000). However, these agents have the major liability of an enhanced risk of proarrhythmia at slow heart rates. For example, torsades de points has been observed when these compounds are utilized (Roden, D.M. "Current Status of Class III Antiarrhythmic Drug Therapy", *Am J. Cardiol.*, 72:44B-49B, 1993).

5 This exaggerated effect at slow heart rates has been termed "reverse frequency-dependence", and is in contrast to frequency-independent or forward frequency-dependent actions (Hondegheem, L.M. "Development of Class III Antiarrhythmic Agents". *J. Cardiovasc. Cardiol.*, 20 (Suppl. 2):S17-S22). Amiodarone has been shown to possess interesting Class III properties (Singh B.N., Vaughan Williams E.M. "A Third Class Of Anti-Arrhythmic Action: Effects On Atrial
10 And Ventricular Intracellular Potentials And Other Pharmacological Actions On Cardiac Muscle, of MJ 1999 and AH 3747" *Br. J. Pharmacol.*, 39:675-689, 1970; Singh B.N., Vaughan Williams E. M., "The Effect Of Amiodarone, A New Anti-Anginal Drug, On Cardiac Muscle", *Br. J. Pharmacol.*, 39:657-667, 1970), although it is not a selective Class III agent because it effects multiple ion channels; additionally, its use is severely limited due to its side effect profile
15 (Nademanee, K. "The Amiodarone Odyssey". *J. Am. Coll. Cardiol.*, 20:1063-1065, 1992; Fuster et al, *Circulation*, 104:2118-2150, 2001; Bril, A. *Curr. Opin. Pharmacol.* 2:154-159, 2002). Thus, currently available agents such as amiodarone and Class III drugs confer a significant risk of adverse effects including the development of potentially lethal ventricular proarrhythmia.

20 The ultrarapid delayed rectifier K^+ current, I_{Kur} , has been observed specifically in human atrium and not in ventricle. The molecular correlate of I_{Kur} in the human atrium is the potassium channel designated Kv1.5. Kv1.5 mRNA (Bertaso, Sharpe, Hendry, and James, *Basic Res. Cardiol.*, 97:424-433, 2002) and protein (Mays, Foose, Philipson, and Tamkun, *J. Clin. Invest.*, 96:282-292, 1995) has been detected in human atrial tissue. In intact human atrial
25 myocytes, an ultra-rapidly activating delayed rectifier K^+ current (I_{Kur}), also known as the sustained outward current, I_{sus} or I_{so} , has been identified and this current has properties and kinetics identical to those expressed by the human K^+ channel clone (hKv1.5, HK2) [Wang, Fermi and Nattel, *Circ. Res.*, 73:1061-1076, 1993; Fedida et al., *Circ. Res.* 73:210-216, 1993; Snyders, Tamkun and Bennett, *J. Gen. Physiol.*, 101:513-543, 1993] and a similar clone from rat
30 brain (Swanson et al., *Neuron*, 4:929-939, 1990). Furthermore, because of its rapidity of activation and limited slow inactivation, I_{Kur} is believed to contribute significantly to repolarization in human atrium. Consequently, a specific blocker of I_{Kur} , that is a compound which blocks Kv1.5, would overcome the shortcoming of other compounds by prolonging refractoriness through retardation of the repolarization in the human atrium without causing the
35 delays in ventricular repolarization that underlie arrhythmogenic afterdepolarizations and

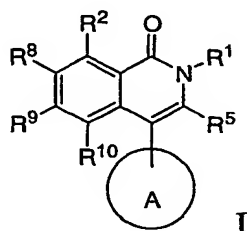
acquired long QT syndrome observed during treatment with current Class III drugs. Kv1.5 blockers exhibiting these properties have been described (Peukert et al, *J. Med. Chem.*, 46:486-498, 2003; Knobloch et al, *Naunyn-Schmedieberg's Arch. Pharmacol.* 366:482-287, 2002; Merck & Co., Inc. WOO224655, 2002).

5 The compounds described in this invention represent a novel structural class of Kv1.5 antagonist.

SUMMARY OF THE INVENTION

This invention relates to potassium channel inhibitors of general structural

10 Formula I

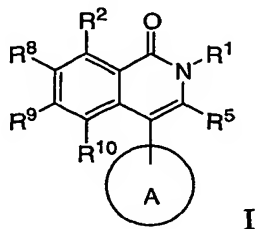


The compounds of this invention are useful in the treatment and prevention of cardiac arrhythmias, and the like. Also within the scope of this invention are pharmaceutical formulations comprising a compound of Formula I and a pharmaceutical carrier.

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DETAILED DESCRIPTION OF THE DISCLOSURE

The invention is a compound of formula I



or a pharmaceutically acceptable salt, crystal form, or hydrate, wherein:

20 A is

a) an aryl ring, wherein any stable aryl ring atom is independently unsubstituted or substituted with

- 1) halogen,
- 2) NO₂,

- 3) CN,
- 4) $\text{CR}^{46}=\text{C}(\text{R}^{47}\text{R}^{48})_2$,
- 5) $\text{C}\equiv\text{C R}^{46}$,
- 6) $(\text{CR}^i\text{R}^j)_r\text{OR}^{46}$,
- 7) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46}\text{R}^{47})$,
- 8) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{R}^{46}$,
- 9) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{OR}^{46}$,
- 10) $(\text{CR}^i\text{R}^j)_r\text{R}^{46}$,
- 11) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_{0-2}\text{R}^{61}$,
- 12) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_{0-2}\text{N}(\text{R}^{46}\text{R}^{47})$,
- 13) $\text{OS}(\text{O})_{0-2}\text{R}^{61}$,
- 14) $\text{N}(\text{R}^{46})\text{C}(\text{O})\text{R}^{47}$,
- 15) $\text{N}(\text{R}^{46})\text{S}(\text{O})_{0-2}\text{R}^{61}$,
- 16) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}$,
- 17) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}\text{OR}^{47}$,
- 18) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})(\text{CR}^k\text{R}^l)_s\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$,
- 19) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{R}^{61}$,
- 20) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{47}\text{R}^{48})$,
- 21) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$, or
- 22) oxo, or

b) a heteroaryl ring selected from the group consisting of

a 5-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O or S,

a 6-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O and S, and

a 9- or 10-membered unsaturated bicyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O or S;

wherein any stable S heteroaryl ring atom is unsubstituted or mono- or di-substituted with oxo, and any stable C or N heteroaryl ring atom is independently unsubstituted or substituted with

- 1) halogen,
- 2) NO_2 ,
- 3) CN,

- 4) $\text{CR}^{46}=\text{C}(\text{R}^{47}\text{R}^{48})_2$,
- 5) $\text{C}\equiv\text{CR}^{46}$,
- 6) $(\text{CR}^i\text{R}^j)_r\text{OR}^{46}$,
- 7) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46}\text{R}^{47})$,
- 8) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{R}^{46}$,
- 9) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{OR}^{46}$,
- 10) $(\text{CR}^i\text{R}^j)_r\text{R}^{46}$,
- 11) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_{0-2}\text{R}^{61}$,
- 12) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_{0-2}\text{N}(\text{R}^{46}\text{R}^{47})$,
- 13) $\text{OS}(\text{O})_{0-2}\text{R}^{61}$,
- 14) $\text{N}(\text{R}^{46})\text{C}(\text{O})\text{R}^{47}$,
- 15) $\text{N}(\text{R}^{46})\text{S}(\text{O})_{0-2}\text{R}^{61}$,
- 16) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}$,
- 17) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}\text{OR}^{47}$,
- 18) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})(\text{CR}^k\text{R}^l)_s\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$,
- 19) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{R}^{61}$,
- 20) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{47}\text{R}^{48})$,
- 21) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$, or
- 22) oxo;

R^1 is selected from the group consisting of

- 1) hydrogen,
- 2) $(\text{CR}^a\text{R}^b)_n\text{R}^{40}$
- 3) $(\text{CR}^a\text{R}^b)_n\text{OR}^{40}$,
- 4) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40}\text{R}^{41})$,
- 5) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40})\text{C}(\text{O})\text{OR}^{41}$,
- 6) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40})(\text{CR}^c\text{R}^d)_2\text{N}(\text{R}^{41})\text{C}(\text{O})\text{R}^{49}$,
- 7) C_{3-8} cycloalkyl,
- 8) $(\text{CR}^a\text{R}^b)_n\text{C}(\text{O})\text{OR}^{40}$,
- 9) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40})(\text{CR}^c\text{R}^d)_{1-3}\text{R}^{41}$,
- 10) $(\text{CR}^a\text{R}^b)_n\text{S}(\text{O})_{0-2}\text{R}^6$,
- 11) $(\text{CR}^a\text{R}^b)_n\text{S}(\text{O})_{0-2}\text{N}(\text{R}^{40}\text{R}^{41})$,
- 12) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40})\text{R}^6\text{OR}^{41}$,
- 13) $(\text{CR}^a\text{R}^b)_n\text{N}(\text{R}^{40})(\text{CR}^c\text{R}^d)_{0-6}\text{C}(\text{O})\text{N}(\text{R}^{41}\text{R}^{42})$;

R^5 is selected from the group consisting of

1) C(O)N(R⁵⁵R⁵⁰),

2) C(O)OR⁵⁵, and

3) C(O)R⁸²;

R², R⁸, R⁹ and R¹⁰ are independently selected from:

1) hydrogen,

2) halogen,

3) NO₂,

4) CN,

5) CR⁴³=C(R⁴⁴R⁴⁵),

6) C≡CR⁴³,

7) (CR^eR^f)_pOR⁴³,

8) (CR^eR^f)_pN(R⁴³R⁴⁴),

9) (CR^eR^f)_pC(O)R⁴³,

10) (CR^eR^f)_pC(O)OR⁴³,

11) (CR^eR^f)_pR⁴³,

12) (CR^eR^f)_pS(O)₀₋₂R⁶⁰,

13) (CR^eR^f)_pS(O)₀₋₂N(R⁴³R⁴⁴),

14) OS(O)₀₋₂R⁶⁰,

15) N(R⁴³)C(O)R⁴⁴,

16) N(R⁴³)S(O)₀₋₂R⁶⁰,

17) (CR^eR^f)_pN(R⁴³)R⁶⁰,

18) (CR^eR^f)_pN(R⁴³)R⁶⁰OR⁴⁴,

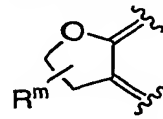
19) (CR^eR^f)_pN(R⁴³)(CR^gR^h)_qC(O)N(R⁴⁴R⁴⁵),

20) N(R⁴³)(CR^eR^f)_pR⁶⁰,

21) N(R⁴³)(CR^eR^f)_pN(R⁴⁴R⁴⁵), and

22) (CR^eR^f)_pC(O)N(R⁴³R⁴⁴),

or R² and R⁸ are independently as defined above, and R⁹ and R¹⁰, together with the atoms to which they are attached, form the ring



, where R^m is C₁₋₆alkyl;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k and R^l are independently selected from the group consisting of:

1) hydrogen,

2) C₁-C₆ alkyl,

- 3) halogen,
4) aryl,
5) R⁸⁰,
6) C₃-C₁₀ cycloalkyl, and
7) OR⁴,

said alkyl, aryl, and cycloalkyl being unsubstituted, monosubstituted with R⁷, disubstituted with R⁷ and R¹⁵, trisubstituted with R⁷, R¹⁵ and R¹⁶, or tetrasubstituted with R⁷, R¹⁵, R¹⁶ and R¹⁷;

R⁴, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵², and R⁵⁵ are independently selected from the group consisting of

- 1) hydrogen,
2) C₁-C₆ alkyl,
3) C₃-C₁₀ cycloalkyl,
4) aryl,
5) R⁸¹,
6) CF₃,
7) C₂-C₆ alkenyl, and
8) C₂-C₆ alkynyl,

said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R¹⁸, disubstituted with R¹⁸ and R¹⁹, tri-substituted with R¹⁸, R¹⁹ and R²⁰, or tetrasubstituted with R¹⁸, R¹⁹, R²⁰ and R²¹;

R⁶, R⁶⁰, R⁶¹, and R⁶² are independently selected from the group consisting of

- 1) C₁-C₆ alkyl,
2) aryl,
3) R⁸³, and
4) C₃-C₁₀ cycloalkyl;

said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R²⁶, disubstituted with R²⁶ and R²⁷, tri-substituted with R²⁶, R²⁷ and R²⁸, or tetrasubstituted with R²⁶, R²⁷, R²⁸ and R²⁹;

R⁷, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²⁶, R²⁷, R²⁸, and R²⁹ are independently selected from the group consisting of

- 1) C₁-C₆ alkyl,

- 2) halogen,
- 3) OR⁵¹,
- 4) CF₃,
- 5) aryl,
- 6) C₃-C₁₀ cycloalkyl,
- 7) R⁸⁴,
- 8) S(O)₀₋₂N(R⁵¹R⁵²),
- 9) C(O)OR⁵¹,
- 10) C(O)R⁵¹,
- 11) CN,
- 12) C(O)N(R⁵¹R⁵²),
- 13) N(R⁵¹)C(O)R⁵²,
- 14) S(O)₀₋₂R⁶²,
- 15) NO₂, and
- 16) N(R⁵¹R⁵²);

R⁸⁰, R⁸¹, R⁸², R⁸³, and R⁸⁴ are independently selected from a group of unsubstituted or substituted heterocyclic rings consisting of a 4-6 membered unsaturated or saturated monocyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting N, O and S, and a 9- or 10-membered unsaturated or saturated bicyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O or S; and

n, p, q, r, and s are independently 0, 1, 2, 3, 4, 5 or 6.

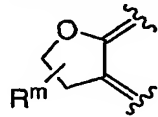
In a class of compounds of the invention, or pharmaceutically acceptable salts thereof,

A is an aryl ring selected from phenyl, unsubstituted or substituted as defined above, or a heteroaryl ring, unsubstituted or substituted as defined above, selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, indole, pyrrolopyridine, benzimidazole, benzoxazole, benzothiazole, and benzoxadiazole;

R², R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of:

- 1) hydrogen,
- 2) halogen,
- 3) OR⁴³, and
- 4) (CR^eR^f)_pR⁴³,

or R² and R⁸ are independently as defined above, and R⁹ and R¹⁰, together with the atoms to which they are attached, form the ring



, where R^m is C₁₋₆alkyl;

R¹ is selected from the group consisting of

- 5 1) hydrogen,
- 2) (CR^aR^b)₁₋₂R⁴⁰
- 3) (CR^aR^b)₁₋₂OR⁴⁰,
- 4) (CR^aR^b)₁₋₂N(R⁴⁰R⁴¹),
- 5) (CR^aR^b)₁₋₂N(R⁴⁰)C(O)OR⁴¹,
- 10 6) (CR^aR^b)₁₋₂N(R⁴⁰)(CR^cR^d)₂N(R⁴¹)C(O)R⁴⁹,
- 7) (CR^aR^b)₁₋₂C(O)OR⁴⁰,
- 8) (CR^aR^b)₁₋₂N(R⁴⁰)(CR^cR^d)₁₋₃R⁴¹, and
- 9) cyclopropyl.

15 In a subclass of the class of compounds, or pharmaceutically acceptable salts thereof,

R², R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of

- 1) hydrogen,
- 2) halogen, and
- 20 3) (CR^eR^f)_pOR⁴³.

In a group of the subclass of compounds, or pharmaceutically acceptable salts thereof,

R¹ is selected from the group consisting of

- 25 1) hydrogen,
- 2) (CR^aR^b)_nR⁴⁰, and
- 3) (CR^aR^b)_nOR⁴⁰.

30 In a subgroup of the group of compounds, or pharmaceutically acceptable salts thereof,

A is an aryl ring, wherein the aryl ring atom is unsubstituted or substituted with halogen; and

R⁵ is selected from the group consisting of

- 1) C(O)N(R⁵⁵R⁵⁰),
- 2) C(O)OR⁵⁵, and
- 3) C(O)R⁸².

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In a family of the subgroup of compounds, or pharmaceutically acceptable salts thereof,

R¹ is -CH₃, -CH₂CHCH₂, or cyclopropyl;

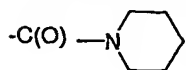
R² and R¹⁰ are hydrogen;

10 R⁸ is hydrogen or -OCH₃;

R⁹ is hydrogen or -OCH₃; and

R⁵ is selected from the group consisting of

-C(O)N(CH₃)₂, -C(O)NH₂, -C(O)OCH₃, -C(O)OH, -C(O)OCH₂CH₃, and



15

A preferred embodiment is a compound selected from the group consisting of

4-(3-fluorophenyl)-6-methoxy-n,n,2-trimethyl-1-oxo-1,2-dihydroisoquinoline-3-carboxamide,

4-(3-fluorophenyl)-6-methoxy-2-methyl-3-(pyrrolidin-1-ylcarbonyl)isoquinolin-1(2H)-one,

2-allyl-6-methoxy-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxamide,

6-methoxy-2-methyl-4-phenyl-3-pyridin-2-ylisoquinolin-1(2h)-one,

2-cyclopropyl-6-methoxy-4-phenyl-3-(1,3-thiazol-2-yl)isoquinolin-1(2h)-one,

methyl 4-(3-fluorophenyl)-6-methoxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylate,

methyl 6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate,

7-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid,

methyl 7-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate, and

ethyl 2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate,

or a pharmaceutically acceptable salt thereof.

The above-listed compounds are active in one or more of the assays for Kv1.5 described below.

Another embodiment of the invention is a method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by Kv1.5 inhibition, which comprises administering an amount of a compound of Formula I that is effective at inhibiting Kv1.5.

A preferred embodiment is a method of treating or preventing cardiac arrhythmias, e.g. atrial fibrillation, atrial flutter, atrial arrhythmia, and supraventricular tachycardia, in a mammal, which comprises administering a therapeutically effective amount of a compound of Formula I.

Another preferred embodiment is a method of preventing thromboembolic events, such as stroke.

Another preferred embodiment is a method of preventing congestive heart failure.

Another preferred embodiment is a method of treating or preventing immunodepression or a disorder involving immunodepression, such as AIDS, cancer, senile dementia, trauma (including wound healing, surgery and shock) chronic bacterial infection, certain central nervous system disorders, and conditions including resistance by transplantation of organs or tissue, graft-versus-host diseases brought about by medulla ossium transplantation. Within this embodiment is a method for treating or preventing immunodepression by administering a compound of the invention with an immunosuppressant compound.

Another preferred embodiment is a method of treating or preventing gliomas including those of lower and higher malignancy, preferably those of higher malignancy.

Another preferred embodiment is a method for inducing in a patient having atrial fibrillation, a condition of normal sinus rhythm, in which the induced rhythm corresponds to the

rhythm that would be considered normal for an individual sharing with the patient similar size and age characteristics, which comprises treating the patient with a compound of the invention.

Another preferred embodiment is a method for treating tachycardia, (i.e., rapid heart rate e.g. 100 beats per minute) in a patient which comprises treating the patient with an antitachycardia device (e.g. a defibrillator or a pacemaker) in combination with a compound of Claim 1.

The present invention also encompasses a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable crystal form or hydrate thereof. A preferred embodiment is a pharmaceutical composition of the compound of Formula I, comprising, in addition, a second agent.

The compounds of the present invention may have asymmetric centers or asymmetric axes, and this invention includes all of the optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to both isomers.

In addition compounds with carbon-carbon double bonds may occur in Z- and E-forms with all isomeric forms of the compounds being included in the present invention.

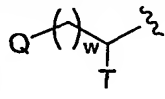
As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms. Commonly used abbreviations for alkyl groups are used throughout the specification, e.g. methyl may be represented by "Me" or CH_3 , ethyl may be represented by "Et" or CH_2CH_3 , propyl may be represented by "Pr" or $\text{CH}_2\text{CH}_2\text{CH}_3$, butyl may be represented by "Bu" or $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, etc. "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. C₁₋₆ alkyl includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C₁₋₄ alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. The term "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

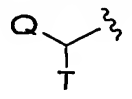
The term "alkenyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a double bond. The alkene ethylene is represented, for example, by CH_2CH_2 or alternatively, by $\text{H}_2\text{C}=\text{CH}_2$. "C₂₋₅ alkenyl" (or "C₂-C₅ alkenyl") for example, means linear or branched chain alkenyl groups having from 2 to 5 carbon atoms and includes all of the pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, 1-propenyl, 2-propenyl, and ethenyl (or ethylenyl). Similar terms such as "C₂₋₃ alkenyl" have an analogous meaning.

The term "alkynyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a triple bond. The alkyne acetylene is represented, for example, by "CHCH" or alternatively, by "HC≡CH". "C₂-5 alkynyl" (or "C₂-C₅ alkynyl") for example, means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of the pentynyl isomers as well as 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C₂-3 alkynyl" have an analogous meaning.

Unless otherwise noted, alkyl, alkenyl and alkynyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl) S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heterocycle, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl.

The term "C₀" as employed in expressions such as "C₀-6 alkyl" means a direct covalent bond. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond.

For example, in the structure , wherein w is an integer equal to zero, 1 or 2, the

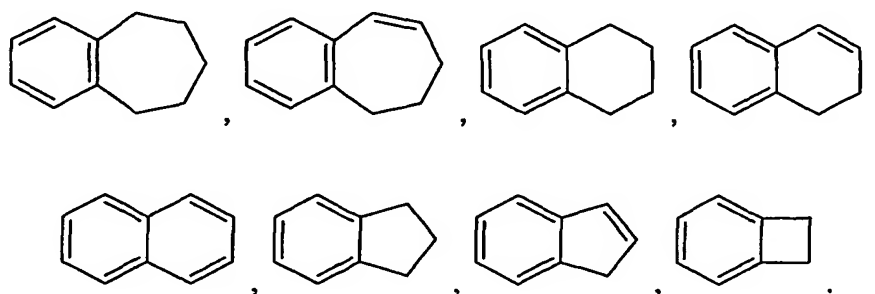
structure is  when w is zero.

The term "C₃-8 cycloalkyl" (or "C₃-C₈ cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C₃-7 cycloalkyl", "C₃-6 cycloalkyl", "C₅-7 cycloalkyl" and the like have analogous meanings.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)).

The term "C₁-6 haloalkyl" (which may alternatively be referred to as "C₁-C₆ haloalkyl" or "halogenated C₁-C₆ alkyl") means a C₁ to C₆ linear or branched alkyl group as defined above with one or more halogen substituents. The term "C₁-4 haloalkyl" has an analogous meaning. The term "C₁-6 fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series (CH₂)₀₋₄CF₃ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C₃ to C₈ monocyclic, saturated or unsaturated ring or (ii) a C₇ to C₁₂ bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent of, or fused to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C₇ to C₁₀ bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which one ring is saturated and the other is saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is saturated is an unsaturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is unsaturated is an unsaturated ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. Unless otherwise noted, carbocycle is unsubstituted or substituted with C₁-6 alkyl, C₁-6 alkenyl, C₁-6 alkynyl, aryl, halogen, NH₂ or OH. A subset of the fused bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenylenyl.

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 7- to 12-membered bicyclic ring system, wherein each ring in (ii) is independent of, or fused to, the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon

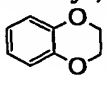
atoms (the monocyclic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

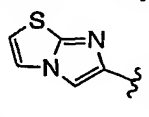

As used herein, the terms "substituted C₃-C₁₀ cycloalkyl", "substituted aryl" and "substituted heterocycle" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl) S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl.

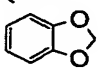
Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl).

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively "heteroaryl") generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalyl, quinazolyl, cinnolyl, chromanyl, isochromanyl, tetrahydroquinolyl, quinolyl, tetrahydroisoquinolyl, isoquinolyl,

2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ) , imidazo(2,1-

5 b)(1,3)thiazole, (i.e., ) , and benzo-1,3-dioxolyl (i.e., ). In certain

contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms.

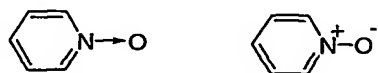
Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C₆ carbocycle" refers to
10 cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

When any variable occurs more than one time in any constituent or in any
15 formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

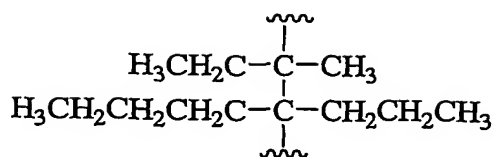
The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent
20 such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

In compounds of the invention having pyridyl N-oxide moieties, the pyridyl-N-oxide portion is structurally depicted using conventional representations such as



25 which have equivalent meanings.

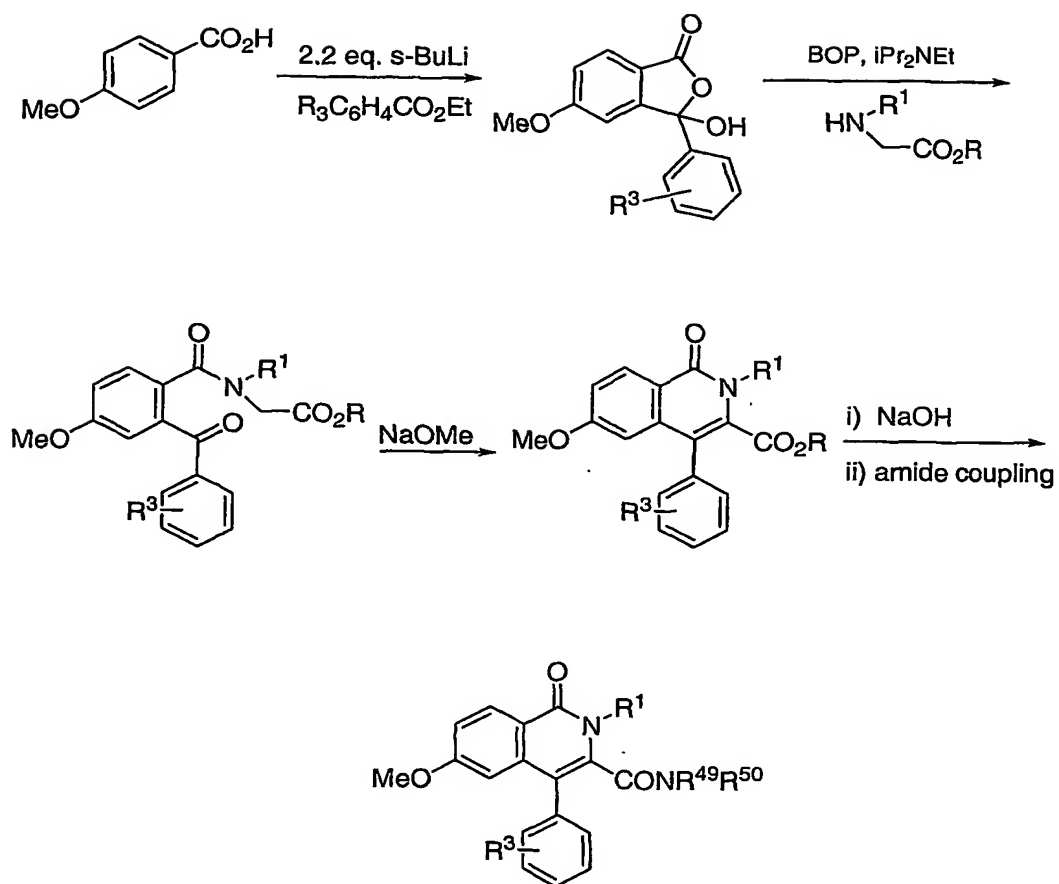
For variable definitions containing terms having repeated terms, e.g., (CRⁱR_j)_r, where r is the integer 2, Rⁱ is a defined variable, and R_j is a defined variable, the value of Rⁱ may differ in each instance in which it occurs, and the value of R_j may differ in each instance in which it occurs. For example, if Rⁱ and R_j are independently selected from the group consisting
30 of methyl, ethyl, propyl and butyl, then (CRⁱR_j)₂ can be



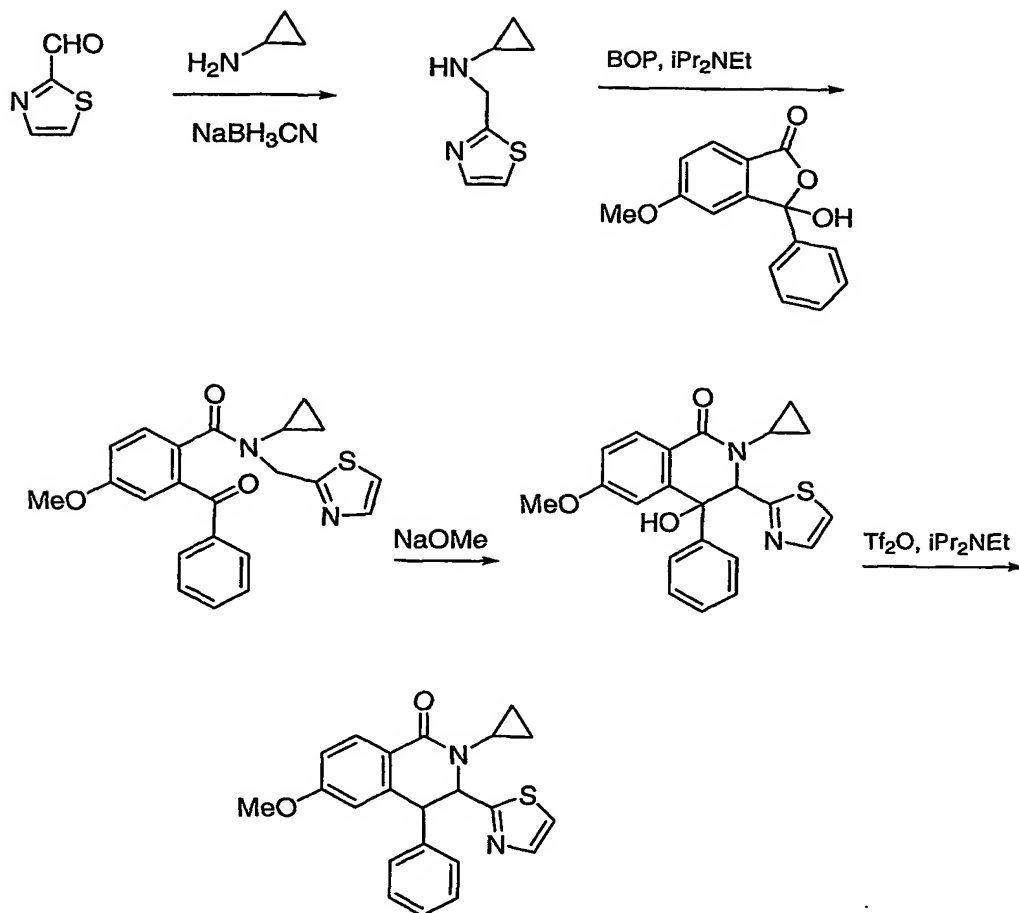
Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydro-scopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or palmoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of Formula I.

Methods for preparing the compounds of this invention are illustrated in the following schemes, in which variables R is hydrogen or C₁-C₆ alkyl, R¹, R⁴⁹, and R⁵⁰ are as defined above, and variable R³ is a substituent selected from the group of substituents listed above as possible substituents when A is a substituted aryl ring. Other synthetic protocols will be readily apparent to those skilled in the art.

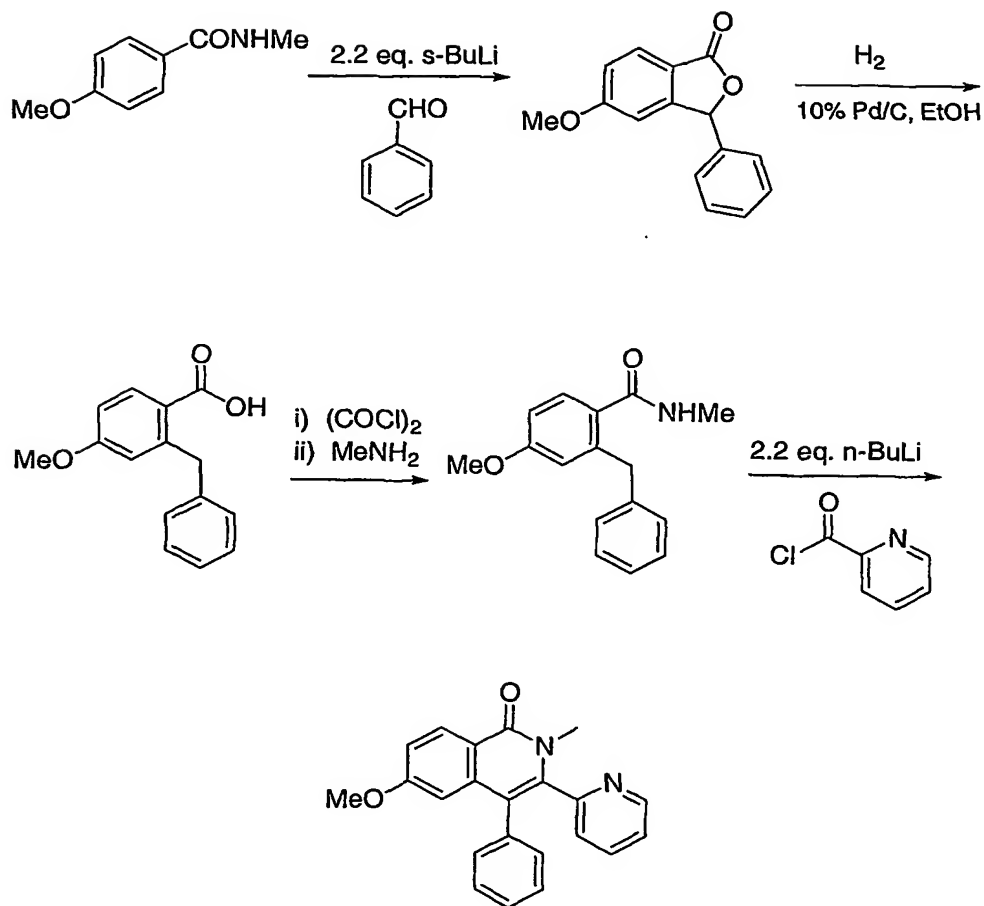
Scheme 1



Scheme 2



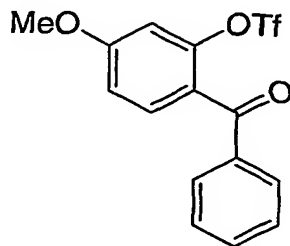
Scheme 3



The following examples illustrate the preparation of the compounds of Formula I and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

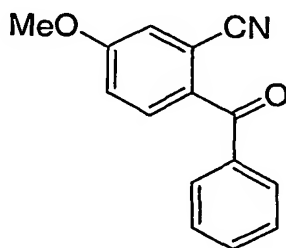
Example I

Preparation of methyl 7-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate (5)



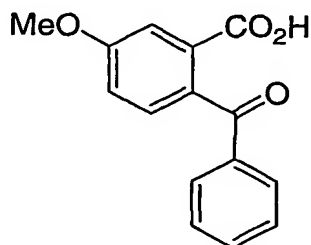
Step A: 4-Methoxy 2-benzoyl-5-methoxyphenyl trifluoromethanesulfonate (1)

Triflic anhydride (9.6 ml, 57 mmol) was added to a solution of (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (10 g, 44 mmol) and triethylamine (10.7 ml, 61 mmol) in methylene chloride (200 ml) at 0 C. The reaction mixture was allowed to warm gradually to room temperature overnight and stirred there overnight. The mixture was then poured onto ice and extracted with ether (500 ml). The extract was washed with 1 N HCl, then water then 10% Na₂CO₃ and dried over Na₂SO₄. Filtration and concentration yielded a dark brown oil. Upon addition of 4:1 hexane / EtOAc (intended chromatography solvent) a white crystalline solid formed. It was filtered off and washed well with a little ether and then some hexane. Drying gave 7.27 g of product as a white crystalline solid. The combined filtrates were evaporated and the residue treated likewise with ether and hexane to give a further 5.95 g of product as a cream colored crystalline solid. Total yield 13.22 g, 84%.



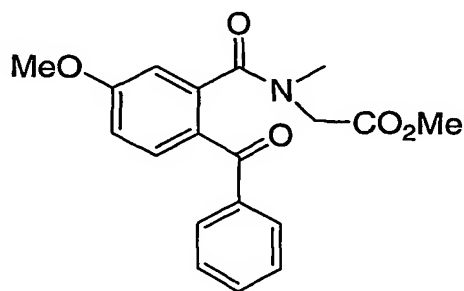
Step B: 2-Benzoyl-5-methoxybenzonitrile (2)

A mixture of the starting triflate 2 (5.95g, 16.5 mmol), Zn(CN)₂ (1.36 g, 11.6 mol) and (Ph₃P)₄Pd (0.76 g, 0.6 mmol) in DMF (20 ml) was heated at 80°C overnight. The reaction mixture was then cooled to RT and diluted with toluene. The mixture was washed twice with 20% aq ammonia and once with brine and then dried (MgSO₄). Concentration gave a yellow oil which was purified by flash chromatography (7:3 hexanes / EtOAc) to give the product 2 as a white crystalline solid. Yield 3.48 g, 89%



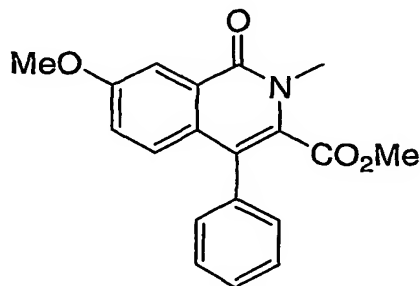
Step C: 2-Benzoyl-5-methoxybenzoic acid (3)

6M HCl (20 ml) was added to a solution of the nitrile 2 (3 g, 12.6 mmol) in dioxane (20 ml). The resulting colorless mixture was heated at 100 C for 3 h. The reaction mixture was then cooled to room temperature and the dioxane removed under reduced pressure to give a white suspension. This suspension was cooled in ice and basified with 2N NaOH. It was extracted with methylene chloride, recooled in ice and acidified with 6M HCl. The resulting white suspension was extracted with methylene chloride, then chloroform then EtOAc. The combined extracts were dried (Na₂SO₄) and concentrated to give the acid 3 as a white powder (3.2 g, 99%).



Step D: Methyl [(2-benzoyl-5-methoxybenzoyl)(methyl)amino]acetate (4)

Hunig's base (1.7 ml, 9.8 mmol) was added to a solution of the acid (0.5 g, 2.0 mmol), amineHCl (0.42 g, 3.9 mmol) and BOP reagent (1 g, 2.3 mmol) in DMF (6 ml) at room temperature. After 1 h there was complete conversion to the amide. The reaction mixture was poured onto ice and extracted with ether. The extracts were washed with aq NaHCO₃, water, 1 N HCl, water, then brine. Drying (Na₂SO₄) and concentration gave the amide 4 as a pale yellow sticky solid.



Step E: Methyl 7-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate (5)

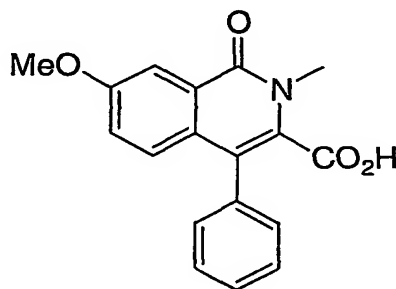
The amide 4 from the previous step was dissolved in methanol (10 ml) and treated with 25% NaOMe in methanol (1 ml). The resulting yellow mixture was then heated at 65 C for 1 h.

- 5 After cooling to room temperature the reaction mixture was acidified with 1M HCl in dioxane. The resulting mixture was filtered to remove NaCl. The filtrate was concentrated and the residue purified by automated flash chromatography.

MS $[M+H]^+$ 324.2

Example II

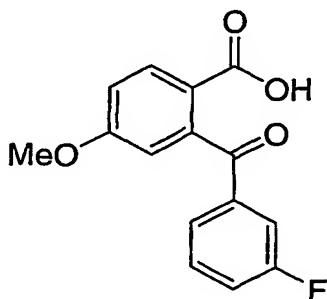
- 10 Preparation of 7-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid (6)



- 15 The ester 5 (180 mg, 0.56 mmol) was suspended in ethanol (5 ml). 1M KOH (1 ml) was added and the resulting mixture heated at 80 C. A homogenous solution was obtained within minutes. After 2h, the reaction mixture was cooled and acidified with 1M HCl. The ethanol was removed under reduced pressure and water was added to the residue. The mixture was filtered and the residue washed well with water and dried to give the acid 6.

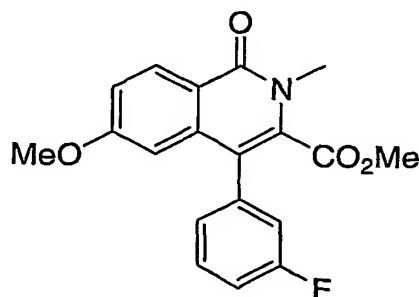
MS $[M+H]^+$ 310.2

Example III

Preparation of methyl 4-(3-fluorophenyl)-6-methoxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (8)5 Step A: 2-(3-Fluorobenzoyl)-5-methoxybenzoic acid (7)

s-Butyllithium (52 mL, 1.4 M in pentane, 72 mmol) was added at -78°C over 90 min. to a solution of p-Anisic acid (5 g, 33 mmol) and TMEDA (11 ml, 72 mmol) in THF (80 mL). After stirring for 15 min. ethyl 3-fluorobenzoate (5 mL, 40 mmol) was added in one portion. The reaction mixture was stirred for 15 min. then it was quenched with water (20 mL).

10 The reaction mixture was then warmed to room temperature poured into water (1.5 L) 1N NaOH (30 ml) was added and the reaction mixture was then extracted with EtOAc. The extracts were discarded. The aqueous phase was then acidified with conc. HCl to pH 1 and extracted with EtOAc. Drying (Na_2SO_4) and concentration gave a residue which was recrystallized from hexanes / EtOAc to give the title compound as a white solid.



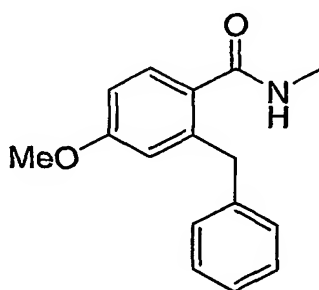
Step B: Methyl 4-(3-fluorophenyl)-6-methoxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (8)

The ester 8 was prepared from the acid 7 essentially according to the procedures described for ester 5 in Example I, Steps D and E.

5 MS [M+H]⁺ 342.2

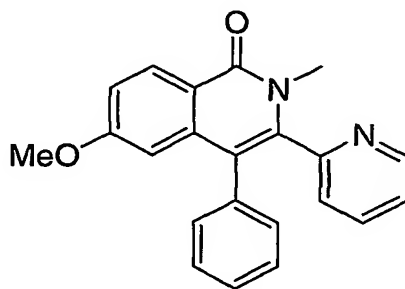
Example IV

Preparation of 6-methoxy-2-methyl-4-phenyl-3-pyridin-2-ylisoquinolin-1(2H)-one (10)



Step A: 2-Benzyl-4-methoxy-N-methylbenzamide (9)

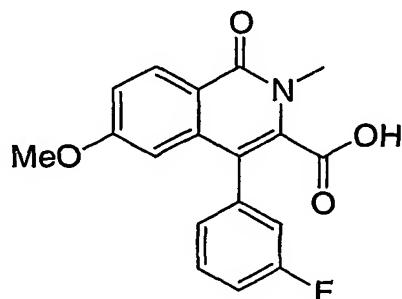
10 The amide 9 was prepared from p-Anisoyl chloride according to published procedures (WO 02/24655)



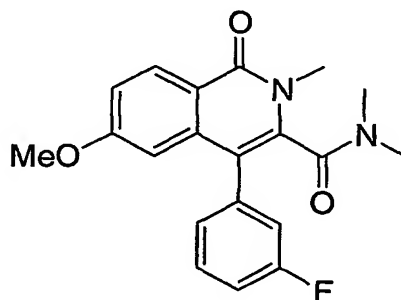
Step B: 6-Methoxy-2-methyl-4-phenyl-3-pyridin-2-ylisoquinolin-1(2H)-one (10)

15 n-BuLi (1.6 M in hexanes, 17.6 mL, 28 mmol) was added to a solution of amide 9 (3g, 12 mmol) in THF (70 mL) at -78 C. After stirring for 30 min, 2-picolyl chloride.HCl (3.1g, 8.8 mmol) was added. After stirring for 30 min the reaction mixture was quenched with water then warmed to room temperature. The reaction mixture was concentrated and the residue partitioned between water and EtOAc. The organic phase was dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography.

20 HRMS (ES) for C₂₂H₁₈N₂O₂, Theoretical 343.1441, Found 343.1449

Example VPreparation 4-(3-fluorophenyl)-6-methoxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid (11)

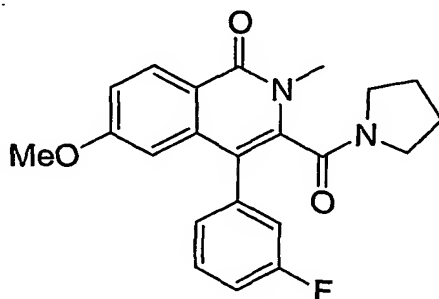
5 The acid 11 was prepared essentially according to the procedure for acid 6 in Example II.

Example VIPreparation of 4-(3-fluorophenyl)-6-methoxy-N,N,2-trimethyl-1-oxo-1,2-dihydroisoquinoline-3-carboxamide (12)

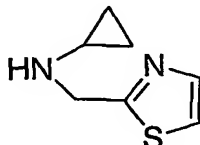
10

The acid chloride of 11 (80 mg, 0.1 mmol) was added to a solution of excess dimethylamine in dichloroethane containing a catalytic amount of DMAP at room temperature. After stirring for 30 min the reaction mixture was washed with 1M HCl then brine. Drying (Na₂SO₄) and concentration gave the amide 12.

15 HRMS (ES) for C₂₀H₁₉N₂O₃F, Theoretical 355.1453, Found 355.1476

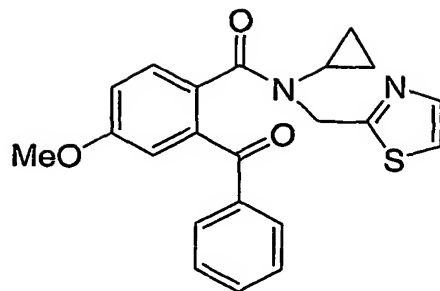
Example VIIPreparation of 4-(3-fluorophenyl)-6-methoxy-2-methyl-3-(pyrrolidin-1-ylcarbonyl)-isoquinolin-1(2H)-one (13)

5 Amide 13 was prepared essentially according to the previous procedure.
HRMS (ES) for C₂₂H₂₁N₂O₃F, Theoretical 381.1609, Found 381.1579

Example VIIIPreparation of 2-cyclopropyl-6-methoxy-4-phenyl-3-(1,3-thiazol-2-yl)isoquinolin-1(2H)-one (17)

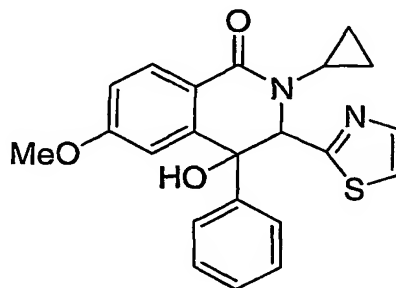
10 Step A: N-(1,3-thiazol-2-ylmethyl)cyclopropanamine (14)

Furan-2-carboxaldehyde (0.37 g, 3.9 mmol) was added to a solution of cyclopropylamine (0.2 g, 3.5 mmol) in methanol (6 mL). After stirring for 1h the reaction mixture was cooled to 0 C and acetic acid (a few drops) and NaBH₃CN (1.5 eq) were added. After stirring for 1h the reaction mixture was concentrated and the residue partitioned between
15 EtOAc and NaHCO₃. The organic layer was dried (MgSO₄) and concentrated and the product purified by flash chromatography (10 – 25% EtOAc / hexanes).



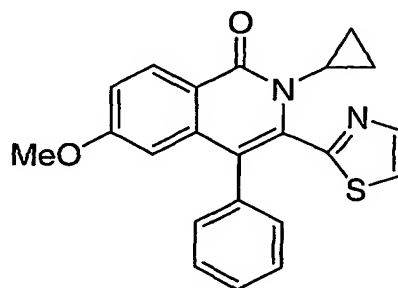
Step B: 2-benzoyl-N-cyclopropyl-4-methoxy-N-(1,3-thiazol-2-ylmethyl)-benzamide (15)

Amide 15 was prepared from amine 14 essentially according to the procedure of Example I, Step D by using the corresponding acid.



Step C: 2-Cyclopropyl-4-hydroxy-6-methoxy-4-phenyl-3-(1,3-thiazol-2-yl)-3,4-dihydroisoquinolin-1(2H)-one (16)

Compound 16 was prepared by cyclization of amide 15 essentially according to the procedure described in Example I, Step E. No spontaneous elimination of water was observed under these conditions.



Step D: 2-cyclopropyl-6-methoxy-4-phenyl-3-(1,3-thiazol-2-yl)isoquinolin-1(2H)-one (17)

Compound 17 was prepared from compound 16 as follows. Pyridine (1.2 eq) and triflic anhydride (1.2 eq) were added sequentially to a solution of 17 (75 mg, 0.19 mmol) in

methylene chloride at -78°C . The reaction mixture was allowed to warm gradually to room temperature. The reaction mixture was then washed with water and dried (MgSO_4).

Concentration gave a residue which was purified by automated flash chromatography.

MS $[\text{M}+\text{H}]^{+}$ 375.2

5 Using the methodologies described below, representative compounds of the invention were evaluated and found to exhibit activity in the Kv1.5 assays, thereby demonstrating and confirming the utility of the compounds of this invention as Kv1.5 inhibitors and antiarrhythmics. Compounds of this type may exhibit forward rate-dependence, blocking the outward K^{+} currents to a greater extent or preferentially at faster rates of depolarization or heart
10 rates. Such a compound could be identified in electrophysiological studies as described below. For example, during a train of depolarizations delivered at frequencies of 1 Hz and 3 Hz, the block is "rate-dependent" if the amount of block observed during a 10 second train at 3 Hz is greater than that at 1 Hz. A Kv1.5 blocker may also display use-dependence, during which the block of the outward K^{+} currents increases with use, or during repetitive depolarization of a
15 cardiac cell. Use dependence of block occurs to a greater extent with each successive depolarization in a train or sequence of pulses or depolarizations at a given rate or frequency. For example, during a train of 10 depolarizations at a frequency of 1 Hz, the block is "use-dependent" if the amount of block is greater for the 10th pulse than for the 1st pulse of the train. A Kv1.5 blocker may exhibit both use-dependence and rate-dependence.

20 A Kv1.5 blocker may also be identified through electrophysiological studies of native I_{Kur} using cardiac myocytes or other tissue from various species including, but not limited to, human, rat, mouse, dog, monkey, ferret, rabbit, guinea pig, or goat. In native tissues Kv1.5 may exist as a homo-oligomer, or as a hetero-oligomer with other Kv family members, or may exist in a complex with a β -subunit. Compounds of this invention may block Kv1.5 homo- or
25 hetero-oligomers or Kv1.5 in complexes with β -subunits.

Kv1.5 assays

 The high throughput Kv1.5 planar patch clamp assay is a systematic primary screen. It confirms activity and provides a functional measure of the potency of agents that
30 specifically affect Kv1.5 potassium channels. Kiss et al. (Assay and Drug Dev. Tech., 1(1-2):127-135, 2003) and Schroeder et al. (J. of Biomol. Screen., 8(1);50-64, 2003) describe the use of this instrument for Kv1.5 as well as other voltage gated ion channels.

 Chinese hamster ovary cells (CHO) stably expressing the human Kv1.5 potassium channel alpha subunit, cloned from human heart, are grown to 90-100% confluence in Ham's F12

medium supplemented with 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin, 1000 µg/ml G-418 sulfate. Cells are subcultured by treatment with Versene, then suspended in phosphate-buffered saline (PBS) and centrifuged. The cell pellet is resuspended in PBS and the resulting suspension placed in the cell reservoir of the IonWorksTM HT instrument.

5 Electrophysiological recordings are performed with intracellular solution containing (mM): K-gluconate 100, KCl 40, MgCl₂ 3.2, EGTA 3, *N*-2-hydroxyethylpiperazine-*N*¹-2-ethanesulphonic acid (HEPES) 5, adjusted to pH 7.3. Amphotericin (Sigma) is prepared as 30 mg/ml stock solution and diluted to a final working concentration of 0.1 mg/ml in internal buffer solution. The external solution is Dulbecco's PBS (Invitrogen) and contains (mM): CaCl₂ 10
10 0.90, KCl 2.67, KPO₄ 1.47, MgCl₂ 0.50, NaCl 138, NaPO₄ 8.10 and has a pH of 7.4. All compounds are prepared as 10 mM stock solutions in DMSO. Compounds are diluted into external buffer, then transferred from the drug plate to the Patchplate during the experiment (final DMSO concentration <0.66% vol.).

15 Kv1.5 ionic currents are recorded at room temperature. Membrane currents are amplified (RMS ~10pA) and sampled at 10 kHz. Leak subtraction was performed in all experiments by applying a 160 ms hyperpolarizing (10 mV) pre-pulses 200 ms before the test pulses to measure leak conductance. The patch clamp stimulus protocol is as follows:

1. Patchplate wells are loaded with 3.5 µL of external buffer.
2. Planar micropipette hole resistances (R_p) is determined by applying a 10 mV, 160 ms
20 potential difference across each hole (Hole test).
3. Cells are pipetted into the Patchplate and form high resistance seals with the 1-2 µm holes at the bottom of each Patchplate well. A seal test scan is performed to determine how many of the Patchplate wells have cells that have formed seals.
4. In order to gain electrical access to the cells, intracellular solution containing
25 amphotericin is circulated for 4 minutes on the bottom side of the Patchplate.
5. Pre-compound addition test pulse is applied to each well on the Patchplate. Protocol: Cells are voltage clamped at a membrane holding potential of -80 mV for 15 seconds. This is followed by application of a 5 Hz stimulus train (27 x 150 ms depolarizations to +40 mV). The membrane potential steps to +40 mV evoke outward (positive) ionic
30 currents.
6. Compound is added to each well of the Patchplate. Compounds are allowed to incubate for 5 minutes.
7. Post-compound addition test pulse protocol is applied. Protocol: Cells are voltage
35 clamped at a membrane holding potential of -80 mV for 15 seconds. This is followed by application of a 5 Hz stimulus train (27 x 150 ms depolarizations to +40 mV).

Data analysis is conducted off-line. Paired comparisons between pre-drug and post-drug additions are used to determine the inhibitory effect of each compound. % inhibition of the peak control current during the 27th depolarization to +40 mV (in the 5 Hz train) is plotted as a function of antagonist concentration. The concentrations of drug required to inhibit current by 50 % (IC₅₀) are determined by fitting of the Hill equation to the concentration response data:

$$\% \text{ of Control} = 100 \times (1 + ([\text{Drug}]/\text{IC}_{50})^p)^{-1}$$

For each cell four arithmetic metrics are obtained:

- 1) seal resistance
- 2) baseline metric (the mean current at -70 mV from 5 to 45 ms before the first depolarization to +40 mV)
- 3) current run up metric (pre-compound mean current amplitude during the 1st depolarization to +40 mV minus the pre-compound mean current amplitude during the 27th depolarization to +40 mV)
- 4) peak current (maximum current amplitude during the 27th depolarization to +40 mV during the 5 Hz train).

All metrics are obtained during both the pre- and post-compound addition traces. Cells are eliminated from further analysis if:

- 1) seal resistance is <50 MΩ
- 2) baseline metric is >±100 pA during the pre-compound
- 3) current run up metric is >-0.2 nA
- 4) pre-read peak metric is <400 pA.

The above-listed compounds provide ≥ 20% inhibition at a concentration of 33 μM or less in the high throughput Kv1.5 planar patch clamp assay described above.

Atomic Absorption Spectroscopy Protocol:

This assay identifies agents that specifically block the human Kv1.5 K⁺ channel heterologously expressed in CHO cells as measured by Rb⁺ efflux using Flame Atomic Absorption Spectroscopy (FAAS). The application of FAAS for measuring ion channel activity was adapted from Terstappen *et al*, *Anal. Biochem.*, 272:149-155, 1999.

CHO cells expressing human Kv1.5 are cultured as described above, then harvested with trypsin-EDTA and washed with medium.

1. 40,000 cells per well are seeded in a 96-well cell culture plate (assay plate) and the cells are allowed to grow for 48 hours at 37°C.
2. The medium is removed and 200 μl of Rb Load Buffer (Aurora Biomed, Vancouver, BC) is added for 3 hours at 37°C under 5% CO₂.

3. The cells are washed 5 times with 200 μ l Hank's Balanced Salt Solution (HBSS) followed by the addition of 100 μ l HBSS containing test compound or 0.5 % DMSO.
4. After 10 min, 100 μ l of HEPES-buffered saline containing 140 mM KCl is added and plate is incubated at RT for 5 min. with gentle shaking.
5. Immediately thereafter, 150 μ l of supernatant is transferred to a fresh 96 well plate and the remaining supernatant aspirated.
6. 120 μ l of Cell Lysis Buffer (Aurora Biomed, Vancouver, BC) is added to the assay plate and shaken for 10 min. prior to analysis.
7. Rb content is measured in samples of supernatant (SUP) and lysate (LYS) using an ICR-8000 automated AAS instrument (Aurora Biomed, Vancouver, BC).

% FLUX=100%*(SUP/(LYS+SUP)). % INH=100%*(1-(A-B)/(C-B)), where A is % FLUX in the presence of tested compound, B is % FLUX in the presence of 10 mM (6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)-*N,N*-dimethylmethanaminium chloride, C is % FLUX in the presence of 0.25% DMSO.

The above-listed compounds provide $\geq 25\%$ inhibition at a concentration of 25 μ M or less in the AAS assay described above.

The compounds of this invention can be administered for the treatment or prevention of afflictions, diseases and illnesses according to the invention by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1-500 milligrams per day. Ordinarily, from 10 to 100 milligrams per day in one or

more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment and prevention of afflictions, diseases and illnesses described above, e.g., cardiac arrhythmias such as atrial fibrillation, atrial flutter, atrial arrhythmia, and supraventricular tachycardia, thromboembolic events such as stroke and congestive heart failure, and
5 immunodepression.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or
10 solutions. Other dosage forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

15 Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and
20 protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related
25 sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts
30 and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be
35 conveniently delivered in the form of an aerosol spray presentation from pressurized packs or

nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should

be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

Compounds of the invention can be administered as the sole active ingredient or
5 in combination with a second active ingredient, including other antiarrhythmic agents having Kv1.5 blocking activities such as quinidine, propafenone, ambasilide, amiodarone, flecainide, sotalol, bretylium, dofetilide, almokalant, bepridil, clofilium, other compounds having Kv1.5 blocking activities such as clotrimazole, ketoconazole, bupivacaine, erythromycin, verapamil, nifedipine, zatebradine, bisindolylmaleimide, or other cardiovascular agents such as, but not
10 limited to, ACE inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril erbumine, quinapril, ramipril, andtrandolapril, angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, cardiac glycosides such as digoxin, L-type calcium channel blockers, T-type calcium channel blockers, selective and nonselective beta blockers, an immunosuppressant compound, endothelin
15 antagonists, thrombin inhibitors, aspirin, nonselective NSAIDs other than aspirin such as naproxen, warfarin, factor Xa inhibitors, low molecular weight heparin, unfractionated heparin, clopidogrel, ticlopidine, IIb/IIIa receptor antagonists such as tirofiban, 5HT receptor antagonists, integrin receptor antagonists, thromboxane receptor antagonists, TAFI inhibitors and P2T receptor antagonists. Compounds of the invention can also be administered as the sole active
20 ingredient or in combination with a pacemaker or defibrillator device.